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tify clearly the size of vessels that are assumed to be involved with spasm. Spasm is identified with epicardial arteries, and if not described by site, its epicardial location is taken for granted. Also, as discussed, resistance vessels have been accepted as widely dilated with severe obstruction of epicardial arteries. As a proponent of primary spasm of resistance vessels for at least a decade, I can, with a reasonable amount of precision, attest to near absolute conviction in the past that spasm is primary in epicardial arteries and that resistance vessels are widely dilated in ischemic heart disease. Changes in attitude, especially about resistance vessels, are helpful to the concept, but changes should be defined.

If, indeed, Goldhaber et al. implied involvement of both small and large coronary arteries in vasoconstriction, this position seems more in keeping with the physiology of the coronary vasculature than the view that spasm is primary in epicardial arteries. The involvement of the entire arterial tree in vasomotion seems reasonable, as small and large coronary arteries are similar anatomically, are interconnected by neural arcs, and there is evidence that reactive hyperemia of resistance vessels is accompanied by mild vasodilation of epicardial arteries (7).

Primary and Reflex Spasm

The spasm of resistance vessel concept, which attempts to relate spasm to the pathophysiology of the coronary vasculature, also accepts vasoconstriction of both small and large coronary arteries. As symptoms are attributed to spasm of resistance vessels, this spasm is described as primary, and changes in epicardial arteries are listed as reflex. That vasoconstriction of mural, and not epicardial, arteries induces clinical symptoms is suggested by the physiologic role of these arteries. Resistance vessels are designed to modulate flow by active vasomotion, and spasm is considered to represent an exaggerated vasoconstrictive activity of these small arteries. The function of epicardial arteries is to transport blood, and as they contribute only 5% to the resistance of the coronary vascular tree (7), it seems unlikely that their contribution to the constriction of the coronary arterial tree would be a major factor in flow reduction. This, however, does not imply that severe spasm of resistance vessels cannot be accompanied by severe narrowing or spastic closure of epicardial arteries, but such spasm would be moot in the face of prominent spasm of resistance vessels. As evidence that spasm isolated in epicardial arteries probably does not cause symptoms, direct catheter-induced spasm, which may be severe, almost never is described as inducing chest pain (1).

The concept has received little attention, probably because its views differ markedly from the conventional. However, some of the positions might now seem less radical, and there probably is more positive evidence available about the hypothesis (1) than is appreciated. The concept, if valid, should have a very major impact on ischemic heart disease, and it is suggested that its premises should be considered.

H. RICHARD HELLSTROM, MD
Veterans Administration Medical Center
800 Irving Avenue
Syracuse, New York 13210

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Angina Caused by Reduced Vasodilator Reserve of the Small Coronary Arteries. II: Role of Coronary Microcirculation

Cannon et al. coruscatingly demonstrated the possible role of small coronary artery vasoreactivity in the genesis of myocardial ischemia. But, unlike the concept of inappropriate vasoconstriction or spasm in the nonobstructed epicardial coronary vessels, inappropriate subepicardial vasoreactivity causing myocardial ischemia postulated by the authors is based solely on hemodynamic evidence. One must ask then, what is the status of the small coronary arterioles in these patients and if arteriolar vasoconstriction causing ischemia occurs in nonoccluded or partly occluded coronary vessels. The authors failed to address these important questions. During the last decade, a significant body of information related to the role of coronary small vessel disease in causing angina has been accumulated. Myocardial biopsy and especially autopsy studies have shown that the small coronary arteries are the site of clinically significant disease more often than is generally realized. Progressive occlusion of many small vessels may cause impaired effective perfusion pressure (1). Small vessel resistance caused by small vessel disease remains the most important and controversial factor in regulating regional myocardial perfusion (2,3). Small variations in the luminal diameter of these vessels may cause profound alterations in myocardial blood flow (4).

The authors have included in their group three diabetic patients treated with insulin. In such patients, subepicardial coronary involvement may cause angina (5). Furthermore, of 10 patients with angina and normal arteriograms, Dwyer et al. (6) found 6 patients who had either abnormal glucose tolerance test or a family history of diabetes mellitus. The authors suggested that small coronary arteries may account for the clinical manifestations. The question arises whether subclinical diabetes was present in some of the patients of Cannon et al.

Underlying but unrecognized cardiomyopathy may increase wall tension during diastole and thereby interfere with coronary flow in some patients with overt and subclinical diabetes. Functional derangements in the microcirculation of diabetic patients as a result of small vessel involvement might represent one of the basic causes of myocardial impairment and conduct disturbances (7–12).

By offering original hemodynamic information, Cannon et al.

broaden our ability to look into the poorly explored field of the coronary microcirculation.

SAMUEL ZONERAICH, MD, FACC
Long Island Jewish-Hillside Medical Center
State University of New York at Stony Brook
Queens Hospital Center Affiliation
82-68 164th Street
Jamaica, New York 11432

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Angina Caused by Reduced Vasodilator Reserve of the Small Coronary Arteries. III: Study Design

As an observer of the passing scene of "atypical chest pain," I cannot but be impressed with the multiplicity of claims as to its cause: spasm, thromboemboli, small vessel disease, impaired metabolism, myocardial bridging, and so on. Theories and articles "proving" such theories appear every year, exist for a period of time, are quoted extensively on ward rounds and the like and then usually silently slip into either oblivion or irrelevancy. Before this happens, however, thousands of patients are misclassified, cardiac neuroses are accentuated or supported and hundreds of thousands of research dollars are spent in either attempting to corroborate or negate the results, all in the alleged interest of "science."

In the article by Cannon et al., I am concerned about the inadequately small numbers of patients studied, premature publication of data and inadequate experimental design. Where, for instance, are the data to show that the control subjects at the National Institutes of Health actually do not have the same type of response as was found in the patients with atypical chest pain? Other potential flaws include: 1) the tremendous overlap in the data, with an interpretation by the authors that most conveniently fits the hypothesis, and 2) the possibility that statistically significant differences may not have any biologic significance.

Though this letter may seem unreasonably critical, it is merely stated as it is in order to make a plea to all of us, and especially leaders in medical research, to try and reach some level of sensibility, balance and judgment in research and publications.

KEITH COHN, MD, FACC
Clinical Professor of Medicine
University of California, San Francisco
Co-Director, Division of Cardiology
Pacific Medical Center
P.O. Box 7999
San Francisco, California 94120

Reply

I

Hellstrom draws attention to the possible role of myocardial resistance vessels as mediators of ischemia and infarction (1). Our study does strongly suggest that vasoconstrictor stimuli are capable of either limiting physiologically appropriate arteriolar vasodilation in response to increases in MVO_2 or provoking actual vasoconstriction at rest, resulting in myocardial ischemia and angina. Quite likely, such responses also account for many of the atypical features of chest pain often found in patients with coronary atherosclerosis. Our data also suggest that small vessel vasoconstriction can cause myocardial infarction, in that several of our patients (who had no significant epicardial fixed obstructive disease or spasm) had myocardial infarction, as evidenced by history or by wall motion abnormalities detected by contrast or radionuclide ventriculography.

However, central to Hellstrom's hypothesis is the primary role of resistance vessel spasm in the genesis of myocardial ischemia or infarction, or both, even in the presence of severe coronary atherosclerosis or epicardial coronary spasm. Hellstrom also believes that small and large coronary arteries are similar, both in terms of anatomy and innervation, and that large and small vessel spasm are therefore necessarily manifestations of a single pathophysiologic entity. A natural extension of this is his belief that all cases of Prinzmetal's angina are caused by spasm of resistance vessels, with large vessel spasm being clinically irrelevant and representing only a reflex response to the primary small vessel change.

In regard to these hypotheses, our data do suggest that resistance vessels can constrict in the face of an ischemic (and therefore vasodilator) stimulus. However, we would at this time not ascribe to Hellstrom's unifying hypothesis, which assigns the central causal role of myocardial ischemia and infarction to the resistance vessels in all instances. It is clear that the physiologic response and neural innervation of the epicardial and resistance vessels are different (2); we also believe there is ample evidence demonstrating that large vessel spasm can be profound enough to be primarily responsible for the precipitation of ischemia (3). Although spasm of the resistance vessels may coexist, there is no evidence at this time suggesting that large vessel spasm must necessarily be relegated to a clinically irrelevant role, occurring only reflexly as a result